

Review Article

The Role of Caspases in Parkinson's Disease Pathogenesis: A Brief Look at the Mitochondrial Pathway

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Abstract

Mitochondrial dysfunction plays a vital role in the progression of *Parkinson's Disease (PD)* via inducing activation of Caspases and Caspase cascade. This review focuses on the mitochondrial intrinsic pathway involved in Caspase activation and its participation in PD progression. Oxidative stress, ER stress, environmental toxins, alongside genetic mutations and excitotoxicity can stimulate activation of different pathways including inflammatory, JNK, NFκB and p38 leading to mitochondrial dysfunction and the release of cytochrome C. Subsequently, this leads to the activation of initiator Caspases (-2, -8, -9 and -10), followed by the activation of executioner Caspases (-3, -6 and -7), resulting in dopaminergic cell death and development of PD. This review summarises and updates the most recent findings related to the activation of specific Caspases via different routes focusing on the mitochondrial intrinsic pathway that leads to the destruction of dopaminergic neurons resulting in PD pathogenesis.

Keywords: Parkinson's disease; Caspase; Cascade mitochondria; Oxidative stress; Cytochrome C

Abbreviations

PD: *Parkinson's Disease*; ROS: Reactive Oxidative Species; JNK: *c-Jun-N-terminal kinases*; NFκB: *Nuclear Factor Kappa B*; ER: Endoplasmic Reticulum; mPTP: Permeability Transition Pore of the Mitochondria; PERK: Protein Kinase RNA-like Endoplasmic Reticulum Kinase; UPR: Unfolded Protein Response; AIF: Apoptosis-Inducing Factor; CAD: Caspase-Activated DNA; ICAD: Inhibitory Caspase-activated DNA; Bap31: Bcl-2-Interacting Protein; REK: Rough Endoplasmic Reticulum; UPR: Unfolded Protein Response; PINK1: PTEN-Induced Putative Kinase; IMS: Inner Membrane Space; OMM: Outer Mitochondrial Membrane; LRRK2: Leucine Rich Repeat Kinase2; HTRA2: High Temperature RequirementA2; MAPK: Mitogen Activated Protein kinases; MPTP: 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; DNA-PK: DNA Dependent Protein Kinase

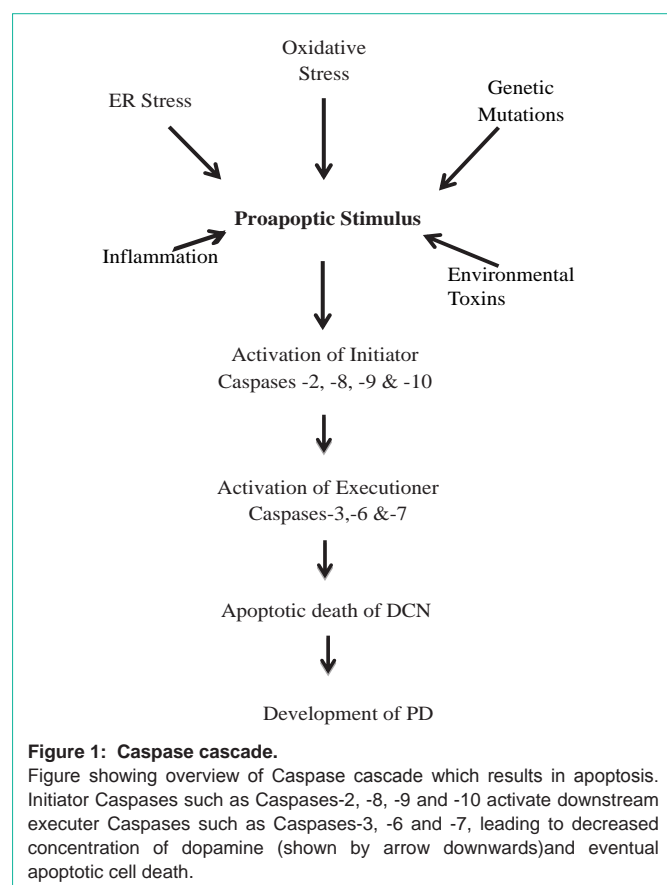
Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterised by tremor, rigidity, Bradykinesia and reduced facial expression. Development of PD is considered to be the result of deficiency of the neurotransmitter dopamine, which is due to death of Dopamine-Containing Neurons (DCNs) that produce dopamine in the *pars compacta* region of the substantia nigra. Although the concentrated efforts of the scientific community over the last decades, the etiology of the death of DCN is yet to be understood. Oxidative stress has been considered as one of the causes of defects in the mitochondria leading to the dopaminergic cell damage [1]. Levodopa therapy is a well-known treatment for the symptoms of PD, however long term use of L-dopa causes side effects including further enhancement of oxidative stress [2]. The elevated levels of Reactive Oxidative Species (ROS) such as hydrogen peroxide, superoxide and hydroxyl ions, induce stimulation to the Permeability Transition

Pore (mPTP) of the mitochondria leading to the collapse of the mitochondrial membrane potential and the release of cytochrome C. Furthermore, increased ROS activity promote nitric oxide binding to superoxide producing peroxynitrate enhancing oxidative and nitrosative stress, which results in DNA damage, chromosomal mutations, lipid peroxidation and enzyme defects [3]. Mutation of E3 ligase caused by peroxynitrate damage leads to impairment of ubiquitin-proteasome system, resulting in high levels of defective proteins, which accumulate in the Endoplasmic Reticulum (ER) promoting ER stress and ultimately cell death. Moreover, the apoptotic neuron triggers injury signals that activate microglia and promote release of cytokines such as interleukins-6 and -8. Subsequently, interleukins trigger Caspase activation along with inducible NO synthase, which further elevates formation of nitric oxide. Exposure to excessive reactive nitrite species along with enhanced production of ROS and peroxynitrate lead to dysfunction of complex-IV and complex-I activities of the mitochondria and promote mitochondrial-mediated apoptosis through Caspase activation [4,5].

Caspases and Parkinson's disease

The loss of DCN within the basal ganglia has been strongly associated with the activation of Caspases (Caspase1-14), a family of cysteine proteases [6-8]. The stimulation of various pathways such as oxidative stress, inflammation, ER stress and toxins promote activation of different Caspases via intrinsic or extrinsic routes, such as mitochondrial or Nuclear Factor Kappa B (NFκB) respectively, leading to death of DCN and PD onset [9]. Caspases can be categorized into two main types; initiator Caspases and executioner Caspases as upstream and downstream respectively. The difference is based on their attributes, such as the role of action and participation in the proteolytic Caspase cascade. Initiator Caspases (Caspase-2,-8,-9 and -10) have long prodomains, which permit joining of proteases to their specific activators [10,11]. Initiator Caspases can activate executioner



Caspases (Caspase-3, -6 and -7), resulting in death of cells via apoptotic routes (Figure 1). Caspase-2 is a unique member of the family as it possesses a dual function, either promoting or suppressing cell death. Moreover, Caspases are able to cleave and activate other members of the Caspase family. An imbalance between active pro-apoptotic and anti-apoptotic proteins results in the development of pathogenesis contributing to apoptosis of DCN that leads to onset of PD [6,10].

The protein, α -synuclein is abundantly found in presynaptic terminals of neurons and in cerebrospinal fluid. It plays a vital role in synaptic maturation and neuronal plasticity. A study conducted by Tai et al (2014) suggested that ROS promote the production of α -synuclein in protein inclusions, contributing to the pathogenesis of PD [12]. Moreover, Smith et al (2005) revealed that mutant α -synuclein can elevate levels of Caspases -3, -9 and -12 along with ROS in differentiated PC12 cells [13]. The mutant α -synuclein has been shown to participate in both ER stress and mitochondrial dysfunction pathways. ER stress stimulates the Unfolded Stress Response (USR), enabling an ER transmembrane kinase PERK (protein kinase RNA-like endoplasmic reticulum kinase) to activate Caspase-12. Subsequently, Caspase-12 activates Caspase-9, followed by stimulation of Caspase-3, resulting in cell death. The α -synuclein combined with mitochondrial impairment interferes with the transport of dopamine contributing to apoptosis and cell destruction. Further support for this view has come from a study conducted by Mizuno and colleagues, which suggested that nigral death, could be the result of elevated levels of oxidative stress and respiratory failure of the mitochondria [5]. Substantial increases of damage in DNA, protein and lipid caused by ROS and oxidative stress has been found

in PD patients. *In vitro* and *in vivo* models of PD confirm increased DNA fragmentation in DCN via induction of Caspase-3 activity [6].

Research by Liou et al (2005) has found a significant rise of Caspases-9, -3 and Calpain activities in MPTP-treated PC12 cells [14]. Calpain is a cytosolic calcium-activated protease, which provokes cleavage and release of Apoptosis-Inducing Factor (AIF) from the mitochondria into the cytosol. AIF adhered to the mitochondrial surface upon entering into the cytosol and promote the release of cytochrome C leading to activation of Caspases-9 and -3 resulting in dopaminergic cell death. Similarly, DNA fragmentation, chromatin condensation and presence of apoptotic bodies have been found in dopaminergic MN9D cells supporting the evidence that dopaminergic cell death follows a mitochondrial-dependent apoptotic pathway. The enhanced release of cytochrome C, alongside impaired ATP levels, encourages the production of ROS, which contributes to further cell death [15].

Caspase-3 catabolises proteins that constitute the cytoskeletal structure, fodrin and actin, resulting in loss of cellular shape alongside loss of cellular adhesion, and contributing to the decrease in cell volume and production of apoptotic bodies. Moreover, Caspase-3 activates Caspases-6 and -7, which play a vital role in cell apoptosis via digestion of specific cellular structures (Figure 2). Caspase-6 promotes the digestion of fibrous proteins, which are essential to nuclear structure and function, such as lamins, causing nuclear shrinkage and budding of the cell, and resulting in the formation of apoptotic bodies. While, Caspase-7 inhibits DNA repair by digesting poly ADP-ribose Polymerase-1 (PARP), Caspase-3 catabolises the DNA repair enzyme DNA dependent Protein Kinase (DNA-PK) into fragments, thereby preventing the cell to repair itself leading to cell death [16-18].

In a healthy cell, the DNAs complex exists in an inactive state and comprises Caspase-activated DNA (CAD) and Inhibitory Caspase Activated DNA (ICAD). Caspase-3 cleaves ICAD from the CAD-ICAD complex, thereby initiating activity of DNase, which promotes catabolism of nuclear DNA and chromatin resulting in decrease in

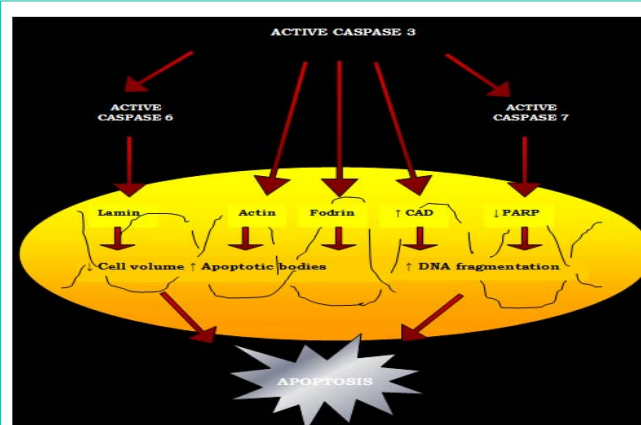


Figure 2: Apoptotic events caused by Caspase-3.

Caspase-3 promotes formation of apoptotic bodies, increased fragmentation of DNA and decreased cell volume via breakdown of actin and fodrin, alongside activation of CAD, Caspases-6 and -7. The formation of apoptotic bodies, chromatin condensation and breakdown of the cell structure, leads to release of ROS which affects neighbouring cells, resulting in mass destruction of DCN and PD pathogenesis.

cell volume and cell death [19,20] (Figure 2). Subsequently, other organelles such as Endoplasmic Reticulum (ER) and Golgi complex are degraded via Caspases by catabolism of Bap31(Bcl-2-interacting protein), a component of a protein complex in the endoplasmic reticulum alongside Golgi membrane proteins [21]. Moreover, the production of ROS during apoptosis promotes further destruction of nearby cells. ROS produced by the apoptotic cells attack the phospholipids bilayer components of adjacent cells, promoting the formation of pores. Subsequently, the ROS penetrate through the pores causing further destruction to the cell via proteolysis of essential proteins and nucleic acid, resulting in further cell death. A mass destruction of DCN caused by prolonged Caspase-activation may contribute to the onset of PD.

Involvement of the intrinsic (mitochondrial) pathway in death of DCN

One of the major pathways that results in Caspase activation is the mitochondrial/intrinsic pathway. The mitochondria play an essential role in ATP production, which is required for many cellular processes to take place. The mitochondrion is comprised of complexes 1-5, which are part of the electron transport chain and embedded in the inner mitochondrial membrane. These complexes are needed to generate ATP. In addition, electron carriers, cytochrome C and coenzyme Q (ubiquinone) are also located in the inner mitochondrial membrane [22]. Cardiolipin is a negatively charged phospholipid located between the inner and outer membranes of the mitochondria. It links cytochrome C to the inner mitochondrial membrane. However, during oxidative stress, the cardiolipin acyl chains are oxidised, allowing the release of cytochrome C from the inner mitochondrial membrane and into the cytosol. In the presence of ATP, cytochrome C induces the zymogen, pro-Caspase-9 to bind to Apaf 1, leading to the activation of Caspase-9. Subsequently, Caspase-9 promotes Caspase-3 activation resulting in cell death [23].

Synaptic terminals have abundance of mitochondria, and mitochondrial fusion to mitochondrial fission ratio is essential in promoting optimal ATP levels and activity of the mitochondria. Preventing mitochondrion fission promotes enlarged size but reduced quantity of mitochondria, decreased oxidative phosphorylation, alongside increased levels of ROS and collapse of mitochondrial membrane potential [20]. Oxidative stress depletes ATP and NADH levels resulting in impairment of complex-I of the mitochondria. Malfunction of the mitochondria leads to defects in ubiquitination, which contributes to the activation of Caspases-1, -3 and -8 [24,25]. Subsequently, the mitochondria's mPTP is opened and cytochrome C is released.

The mitochondrion is very susceptible to oxidative stress; the rise of ROS such as superoxides, hydroxyls and nitric oxide accumulating in DCN promote cleavage of DNA bases via extracting hydrogen atoms and thereby causing a shift in genetic sequence and the generation of mitochondrial mutated genes. Immunofluorescence analysis has shown degeneration of neurons and increase in Caspase activation in knock out PINK-1 in tunicamycin treated rat cortical neurons, indicating a strong link between ER stress, PINK-1 suppression and activation of Caspases [26]. In addition, the lack of histones in mitochondrial DNA, permit mitochondria to be more vulnerable to oxidative stress. The increased levels of hydrogen peroxide, leads to

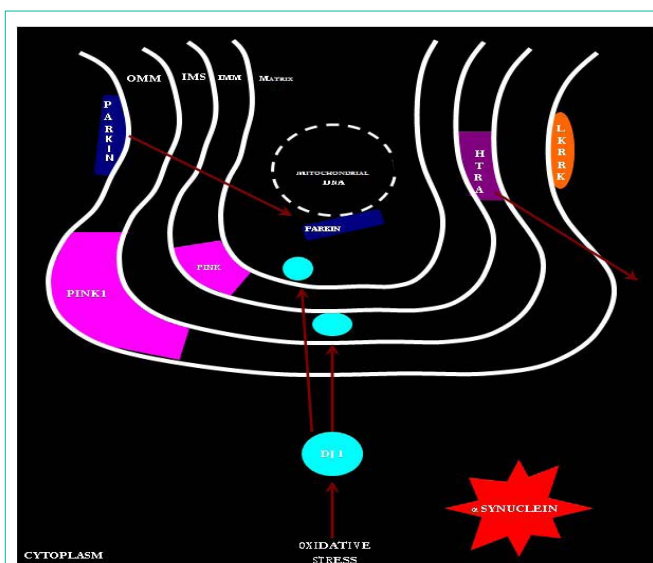


Figure 3: The role of mutant mitochondrial genes PD pathogenesis.

Figure showing the different mutated genes in relation to the mitochondria in PD pathogenesis. Oxidative stress promotes mutated DJ1 gene to travel from the cytoplasm to the IMS and to the mitochondrial matrix, where it allows production of ROS. Mutated HTRA2 is translocated from the IMS to the cytoplasm where it promotes Caspase-mediated death of DCNs via apoptotic pathway. Mutated LRRK2 which is found in the outside of the mitochondrial membrane contributes to toxicity and death of neurons. PINK1 gene is located in the Outer Mitochondrial Membrane (OMM) and IMM functions to decrease ROS levels and suppresses cytochrome C. Mutations of PINK1 and Parkin allow production of ROS and release of cytochrome C, promoting death of cells via apoptotic route.

lipid peroxidation, whilst elevated levels of peroxynitrate result in DNA damage. Reduced levels of DNA polymerase was observed in PD animal model, suggesting suppression of DNA excision repair function [27-29].

Parkinson plays a vital role in maintaining mitochondrial homeostasis, alongside Unfolded Protein Response (UPR) in ER. Mutation of Parkin gene results in ER stress and/or oxidative stress induced cell death. Mutation in Parkin and PINK1 (PTEN-induced putative kinase1) genes has been strongly associated with the progression of PD via mitochondrial-dependent cell apoptosis [28,30] (Figure 3).

A study conducted by Bender et al (2006) revealed the presence of higher levels of mitochondrial DNA deletions in PD patients when compared to the control [31]. DJ-1 is located in various tissues including brain and found in the matrix and Inner Membrane Space (IMS) of the mitochondria, DJ-1 functions as an antioxidant by reducing hydrogen peroxide levels. Frame shift and missense mutations, alongside deletions and insertions of DJ-1 gene, contribute to early PD onset. Mutated DJ-1 leads to increase in oxidative stress and mitochondrial impairment, causing degeneration of DCN, resulting in development of PD [22,27,29] (Figure 3).

LRRK2 (Leucine Rich Repeat Kinase2) also known as dardarin, is associated with nigrostriatal dopamine system, and is found in brain striatum and frontal cortex, located in the outer mitochondrial membrane and cytoplasm (Figure 3). A mutated variant of LRRK2, which is found in the outside of the mitochondrial membrane,

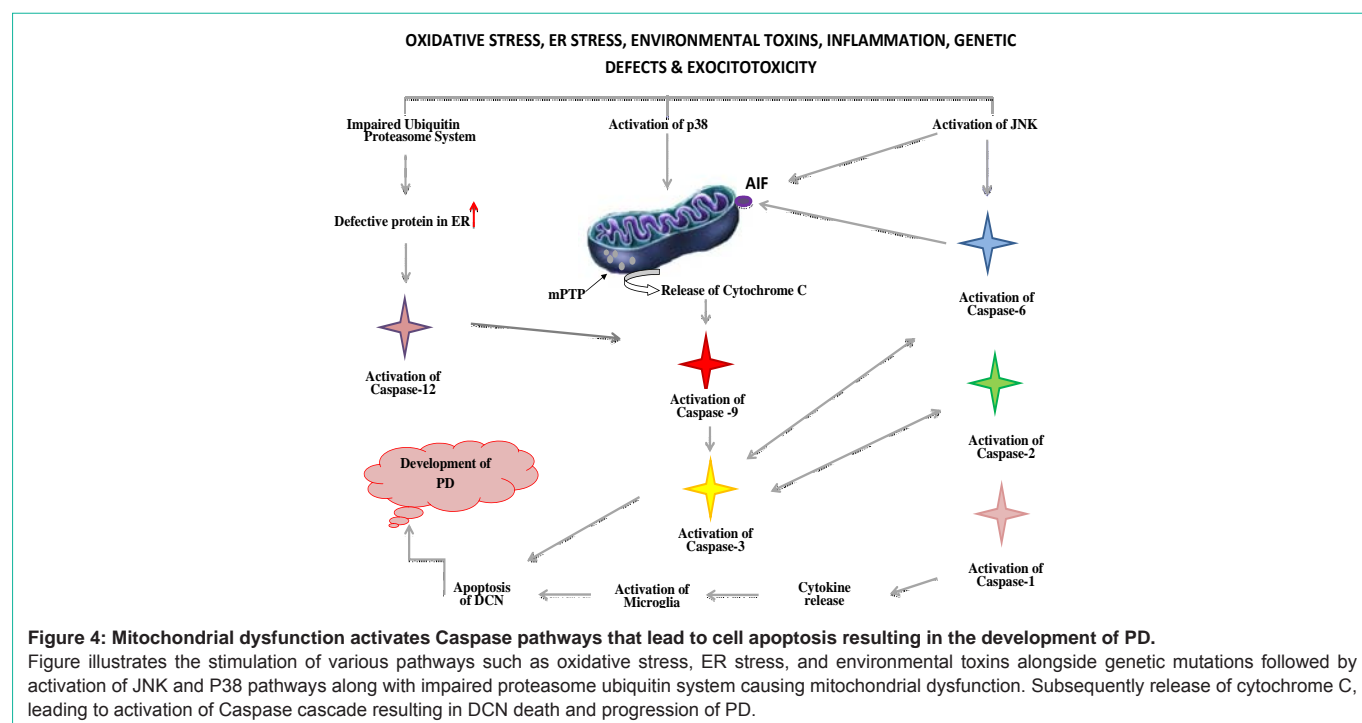


Figure 4: Mitochondrial dysfunction activates Caspase pathways that lead to cell apoptosis resulting in the development of PD.

Figure illustrates the stimulation of various pathways such as oxidative stress, ER stress, and environmental toxins alongside genetic mutations followed by activation of JNK and P38 pathways along with impaired proteasome ubiquitin system causing mitochondrial dysfunction. Subsequently release of cytochrome C, leading to activation of Caspase cascade resulting in DCN death and progression of PD.

contributes to toxicity and death of neurons resulting in late onset of PD [22,27,29].

HTRA2 (High Temperature RequirementA2) is a pro-apoptotic protease found in the IMS of the mitochondria, which plays a vital role in mitochondrial homeostasis. External stimuli such as environmental toxins, provoke HTRA2 gene to translocate from the IMS to the cytoplasm, promoting Caspase-mediated death of cells via apoptotic pathway. Over expression of HTRA2 in mice has shown severe loss of motor neurons via stimulation of the mitochondrial apoptotic pathway, resulting in symptoms similar to that of PD. Moreover, degeneration of striatal neurons caused by stimulation of Caspases has been observed in PD-induced mice [22,27,29] (Figure 3).

Mitochondrial pathway can also be stimulated by activation of C-Jun N-Terminal Kinases (JNK), and p38 pathways. JNK is a group of Mitogen Activated Protein Kinases (MAPK) that play an essential role in apoptosis. Activation of JNK has been strongly associated with development of neurodegenerative disorders, particularly PD [32]. In the JNK pathway, cytochrome C promotes binding of Caspase-9 to the JNK domain forming complexes that stimulate Caspase-9, which in turn cleaves and activates Caspase-3. Liou et al (2005) found that MPTP-induced toxicity caused activation of JNK and promoted stimulation of Caspase pathway in differentiated PC12 cells [14]. Chun et al (2001) demonstrated that MPTP and hydrogen peroxide induced stimulation of JNK pathway, which in turn provoked Caspase-1 and Caspase-3 activation, resulting in apoptosis of clonal nigral dopaminergic cell line SN474 [33]. The study established that Caspase-1 plays a vital role in apoptosis of DCN. In the p38 pathway, cytochrome C promotes binding of the cytosolic protein, AIF to Caspase-9, forming a complex that permits activation of Caspase-9. Subsequently, Caspase-9 stimulates Caspase-3 activity resulting in apoptosis of DCN [34].

The substantial elevated amount of Caspase-2 observed at the

early stage, indicated that Caspase-2 may also contribute to loss of DCN in the early phases of PD [35]. Active Caspase-2 promotes release of cytokines such as interleukin-6 and interleukin-8, leading to stimulation of microglia and death of neuronal cells via apoptotic routes. Oxidative stress, toxicity and mutations of specific genes, such as Parkin E3 ligase can damage the proteasome ubiquitin system resulting in elevated levels of aggregated mis-folded proteins, which accumulate to form Lewy bodies which are abnormal aggregates of protein that develop inside PD's neurons forming one of the hallmark of the disease, bodies alongside stimulating activation of Caspase-12. Active Caspase-12 stimulates Caspase-9, which in turn results in motivation of Caspase-3. Active Caspase-3 promotes fragmentation of DNA, shrinkage cell, formation of apoptotic bodies and death of neuronal cells. The mass destruction of DCN causes degeneration of neurones, resulting in the development of PD (Figure 4).

Conclusion

Caspase family including initiator and executioner Caspases play a vital role in inducing death of dopaminergic neurons, resulting in development and progression of PD. This review highlights the involvement of mitochondrial intrinsic pathway in which exposure to various stimuli such as oxidative stress, inflammation, genetic mutations and environmental toxins trigger the activation of Caspases which suggest their contribution to death of DCNs either by individual activation or via cascade reaction. Understanding the full mechanism of action of Caspase (s) may provide answers to whether using Caspases as a target for inhibition or could reduce cell death of DCN and therefore may aid in the development of potential new treatments for PD.

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